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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-56,59-92 and 95-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,59-92 and 95-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed August 12, 2005. Claims 54-56, 58-92 and 94-115 were previously pending. Applicants cancelled claims 58 and 94, amended claims 54, 76, 77, 79, 80, 82, 83, 86, 87, 90, 91, 111 and 112, and added new claims 116-142. Claims 54-56, 59-92 and 95-142 are pending and will be examined.

2. Applicants' attention is drawn to the fact that claims 74 and 102 have improper claim identifiers, namely, "previously amended" instead of "previously presented", therefore do not comply with 37 CFR 1.121. However, in the interest of advancing the prosecution the amendment will be considered, but Applicants should present claims with proper claim identifiers in the future responses.

3. Applicants' amendments overcame the rejections presented previously. This office action is made non-final because of new grounds for rejection. Applicants' arguments are moot in view of new grounds for rejection.

4. The declaration under 37 CFR 1.132 filed August 12, 2005 has been considered, but is ineffective when considered with respect to the new grounds of rejection presented below. The declaration of Dr. Berezenko states that an unexpected result of higher albumin yield and lower contaminant level was achieved when the concentration of albumin loaded onto the cation exchange column was in the range of 10-250 g/L. However, the declaration presents only three albumin concentrations of 5, 10 and 25 g/L, therefore only two of them fall within the claimed range of 10-250 g/L, and one of them is within the range of 20-70 g/L. Applicants presented data for a 50 g/L sample, but there is no information about the albumin yield for this initial loading concentration, only for the contaminant level. Therefore, it is not clear that the trend of obtaining better albumin yields with increasing loading concentration continues beyond 25 g/L of albumin loading

concentration, and it is not clear how much better are the results concerning contaminant level above 50 g/L. Since Matsuoka et al. teach loading albumin concentration of about 80 g/L, they would inherently achieve the improved results regarding albumin yield and contaminant levels.

Claim Interpretation

5. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted. "Chromatography in the negative mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix. The term "initial albumin solution" is interpreted as the albumin solution before any of the purification steps. The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

6. A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C), therefore claims in which the only difference is reversal of steps will be rejected together, for example, claims 54-75 and 90-110, claims 76-78 and 79-81, claims (82, 84) and (86, 88), claims (83, 85 and 87, 89).

MPEP 2144.04 IV

C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 54-56, 61, 63-65, 74-81, 90-92, 96, 98-100, 109-115, 134-136, 141 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsuoka et al. (EP 0 428 758; cited in the IDS) as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action).

Regarding claims 54, 76, 79, 90, 111, 134, 135, 136, 141 and 142, Matsuoka et al. teach a process for albumin purification (Abstract), the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Matsuoka et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Matsuoka et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points below that of albumin (page 2, lines 53-55; page 3, lines 1-24; page 4, lines 41-48).);

(3) placing the albumin-containing AE product, without further purification, into a final

container for therapeutic use (Matsuoka et al. teach concentrating and heat treatment of the final product to form a theraputic solution, which is aliquoted into containers (page 4, lines 57, 58; page 5, lines 1-8),

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), therefore it contained about 480 g of albumin. Thus, the solution loaded onto the cation exchange column contained about 80 g/L of albumin, anticipating Applicants' range of 10-250 g/L.

Regarding claims 55, 77, 80, 91, 112, 134-136, 141 and 142, Matsuoka et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

> **II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results

in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

Regarding claims 74, 76 and 135, Matsuoka et al. teach subjecting the anion-exchange product to pH-adjustment (page 4, lines 46-48).

Regarding claim 79, 111, 136 and 142, Matsuoka et al. teach subjecting the cation-exchange product to concentration (page 4, lines 57, 58).

Regarding claims 56 and 92, Matsuoka et al. teach CE step utilizing a matrix such as SP-Sepadex (page 3, line 30, 31). Matsuoka et al. do not specifically teach sulfopropyl subsituents as cation exchangers. As evidenced by Ohmura et al., SP stands for a sulfopropyl group, for example, SP-Sephadex is sulfopropyl-dextran (page 5, lines 37-40). Since Matsuoka et al. teach SP-Sepadex, they inherently teach sulfoprpyl groups as cation exchangers.

Regarding claims 61, 78, 81, 96, 109 and 113, Matsuoka et al. teach adjusting the pH of the albumin solution to 5.5 before loading onto CE column (page 3, lines 46-48).

Regarding claims 63 and 98, Matsuoka et al. teach diethylaminoethyl groups as anion exchangers (page 3, line1), therefore they teach dialkylaminoalkyl anion exchangers.

Regarding claims 64 and 99, Matsuoka et al. teach AE step run in a negative mode with respect to albumin (page 4, lines 42-48).

Regarding claims 65 and 100, Matsuoka et al. teach that albumin solution, which undergoes AE chromatography has a pH of 5.1 (page 4, lines 37, 38).

Regarding claims 75 and 110, Matsuoka et al. teach using Cohn fraction V, therefore they teach primary separation of albumin from other cell components (page 4, line 34).

Regarding claims 114 and 115, Matsuoka et al. teach albumin solution of pH of about 4.5 to 5.5 loaded onto CE column (page 4, lines 46-48), therefore Matsuoka et al. teach pH within the

range of 4.5-6.0.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections based on the Matsuoka et al. reference

10. Claims 59-62 and 95-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)) and Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action).

A) Matsuoka et al. do not teach conditioning of albumin solution with octanoate salt prior to cation exchange step.

B) Regarding claims 59-62 and 95-97, Goodey et al. teach addition of sodium octanoate to a final concentration of 1-10 mM (page 16, lines 5-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added sodium octanoate of Goodey et al. to albumin solution of Matsuoka et al. The motivation to do so, provided by Goodey et al., would have been that sodium octanoate protects albumin from polymerization (page 16, lines 7, 8).

11. Claims 116-121 and 130-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc.,

vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)).

A) The teachings of Matsuoka et al. are presented above. Matsuoka et al. teach the concentration of albumin subjected to cation exchange chromatography being about 80 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 116, 118, 120, 130 and 132) or albumin concentration of 50 $\pm$ 10 g/L (claims 117, 119, 121, 131 and 133). However, the upper values of these ranges are very close to the 80 g/L value of Matsuoka et al.

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum

combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 80 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka et al.

Rejections based on Goodey et al. and Matsuoka et al.

12. Claims 54, 59-64, 66, 67, 69-71, 90, 95-99, 101, 102 and 104-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and of Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259,

pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)).

A) Regarding claims 54 and 90, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).)

Regarding claims 59, 60 and 95, Goodey et al. teach initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 61, 62, 96 and 97, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 63 and 98, Goodey et al. teach AE step utilizing a matrix such as DEAE-Spherodex, Q-Hyper D, DEAE-cellulose, QAE-cellulose, TMAE, DMAE, DEAE Fractogel or DEAE Sepharose FF (page 25, lines 12-14). Goodey et al. do not specifically teach dialkylaminoalkyl subsituents as anion exchangers. As evidenced by Ohmura et al., DEAE means diethylaminoethyl group (page 6, lines 11-15), which is a species of dialkylaminoalkyl groups (Lindquist et al., col. 3, lines 53-56). Therefore, since Goodey et al. teach DEAE-Spherodex, DEAE Fractogel or DEAE Sepharose FF, they teach dialkylaminoalkyl subsituents as anion exchangers.

Regarding claims 66 and 101, Goodey et al. teach that solution undergoing anion exchange chromatography has a conductivity of less than 4 mS/cm, namely, 2.5 ± 0.5 mS/cm (page 32, lines 1, 2).

Regarding claims 67 and 102, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claims 69 and 104, Goodey et al. teach ultrafiltration of albumin solution to a concentration between 20-120 g/L or 80-110 g/L before loading onto AE column (page 24, lines 20-24).

Regarding claims 70 and 105, Goodey et al. teach AE column equilibrated with a buffer with conductivity in the range of 1-4 mS/cm or 1.5-5 mS/cm (page 25, line 20; page 32, line 1).

Regarding claims 71 and 106, Goodey et al. teach elution of albumin from CE column with a solution of octanoate (page 31, lines 21-25), which has specific activity for albumin (page 2, lines 1-4). Goodey et al. do not teach elution of albumin from AE column using a solution of octanoate. However, they teach that pH of the eluting solution should be about 5.5, so that the binding of octanoate causes a significant overall charge difference (page 31, lines 23, 24). They also teach

loading the eluate from the cation exchanger onto AE column equilibrated with a buffer of pH 5.5 (page 31, lines 27-29).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Matsuoka et al. teach albumin purification using CE and AE chromatography (Abstract).

Regarding claims 54 and 90, Matsuoka et al. teach a process for albumin purification (Abstract), the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Matsuoka et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Matsuoka et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points below that of albumin (page 2, lines 53-55; page 3, lines 1-24; page 4, lines 41-48).);

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), therefore it contained about 480 g of albumin. Thus, the solution loaded onto the cation exchange

column contained about 80 g/L of albumin, anticipating Applicants' range of 10-250 g/L.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Matsuoka et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have eluted albumin from AE column with a buffer containing a compound having a specific affinity for albumin. The motivation to do so would have been that albumin elution could be accomplished with more specificity and efficiency, since no other proteins bound to a compound with specific affinity for albumin.

13. Claims 68, 72, 73, 103, 107 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946), Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action) and Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action)), as applied to claims 67, 71, 102 and 106 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Claim 68 is drawn to a process according to claim 67 wherein the albumin solution

which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 73 is drawn to the process according to claim 67 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 103 is drawn to a process according to claim 102 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 108 is drawn to the process according to claim 102 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 72 is drawn to a process of claim 71 wherein the buffer comprises 20-90 mM phosphoric acid salt, and claim 107 is drawn to a process of claim 106 wherein the buffer comprises 20-90 mM phosphoric acid salt.

B) Neither Goodey et al. nor Matsuoka et al. teach albumin solution which undergoes positive mode anion exchange chromatography with a pH of 6.0-8.0, or the albumin being eluted in the anion exchange step with a buffer of pH 6.0-8.0. Goodey et al. do not teach albumin elution buffer comprising 20-90 mM phosphoric acid salt.

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8 and salt concentration of 0.001-0.05 M, and eluted from the column using buffer with the same pH range and salt concentration of 0.05 to 1 M (page 6, lines 18-24). They teach anion exchange column buffer of 50 mM phosphate (page 11, lines 49-51). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Matsuoka et al. The motivation to do so, provided by

Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

14. Claims 82, 84, 86, 88, 137 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)) and Matsuoka-2 et al. (U.S. Patent No. 5,277, 818).

A) Regarding claims 82, 86, 137 and 139, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding claims 84 and 88, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

E) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

F) Matsuoka-1 et al. teach albumin purification using CE and AE chromatography (Abstract). Regarding claims 82, 86, 137 and 139, Matsuoka-1 et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(x) collecting the albumin-containing CE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after CE chromatography (page 4, lines 56, 57).);

(xi) subjecting the albumin solution to AE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points below that of albumin (page 2, lines 53-55; page 3, lines 1-24; page 4, lines 41-48).);

(xii) collecting the albumin-containing AE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after AE chromatography (page 4, lines 46-48.),

wherein the albumin solution subjected to cation exchange chromatography in step (1) has

an albumin concentration of 10-250 g/L (Matsuoka-1 et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10th paragraph), therefore it contained about 480 g of albumin. Thus, the solution loaded onto the cation exchange column contained about 80 g/L of albumin, anticipating Applicants' range of 10-250 g/L).

Regarding claims 137 and 139, Matsuoka-1 et al. do not specifically teach that albumin contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka-1 et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

> **II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Matsuoka-1 et al. to

the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka-1 et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka-1 et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

G) Neither Goodey et al. nor Matsuoka-1 et al. teach affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

H) Regarding claims 82, 86, 137 and 139, Matsuoka-2 et al. teach albumin purification using ion exchange and affinity chromatography (Abstract). Matsuoka-2 et al. teach removal of α_1-acid glycoprotein (= glycoconugate) from albumin preparation by affinity chromatography run in a negative mode with respect to albumin (col. 3, lines 38-68; col. 4, lines 1-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed α_1-acid glycoprotein by affinity chromatography of Matsuoka-2 et al. in the method of albumin purification by Goodey et al. and Matsuoka-1 et al. The motivation to do so, provided by Matsuoka-2 et al., would have been that α_1-acid glycoprotein was an impurity having immunosuppressive activity (col. 1, lines 44-46). Therefore, removing α_1-acid glycoprotein from albumin solution according to Matsuoka-2 et al. enhances the ability of Goodey et al. and Matsuoka-1 et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25).

15. Claims 83, 85, 87, 89, 138 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem.

Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)), Matsuoka-2 et al. (U.S. Patent No. 5,277, 818) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Regarding claims 83, 87, 138 and 140, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding steps (xi) and (xii) of claim 83 (or steps (ix) and (x) of claim 87), these are repeated steps (iii) and (iv). Goodey et al. do not specifically teach repeating AE step in a positive

mode with respect to albumin.

Regarding claims 85 and 89, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE chromatography run in a negative mode with respect to albumin.

C) Matsuoka-1 et al. teach albumin purification using CE chromatography (Abstract).

Regarding claims 83, 87, 138 and 140, Matsuoka-1 et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Matsuoka-1 et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points higher than that of albumin, to yield an albumin-containing flow-through (page 3, lines 25-52; page 4, lines 51-57).);

(x) collecting the albumin-containing CE flow through (Matsuoka-1 et al. teach collecting the fluid containing albumin after CE chromatography (page 4, lines 56, 57).),

wherein the albumin solution subjected to cation exchange chromatography in step (1) has an albumin concentration of 10-250 g/L (Matsuoka-1 et al. teach dissolving of 500 g of Cohn fraction V in 4L of solution, loading the solution onto an anion exchange column, recovering the flow-through and adding 2 liters to it before it was loaded onto a cation exchange column (page 4, lines 34-48). As evidenced by Cohn et al., fraction V is about 96% albumin (page 471, 10^{th} paragraph), therefore it contained about 480 g of albumin. Thus, the solution loaded onto the cation exchange column contained about 80 g/L of albumin, anticipating Applicants' range of 10-250 g/L).

Regarding claims 138 and 140, Matsuoka-1 et al. do not specifically teach that albumin

contains glycosylated albumin and that it binds during the cation exchange step. As evidenced by Shaklai et al., 10% of albumin present in human plasma is glycosylated (Abstract). Therefore, since Matsuoka-1 et al. teach subjecting the albumin to the same purification steps as the ones performed by Applicants, they inherently teach binding of the glycosylated albumin to the cation exchange resin (see MPEP 2112-II):

> **II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION**
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. ... *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative mode with respect to albumin of Matsuoka-1 et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Matsuoka-1 et al., would have been that using ion exchange in negative mode with respect to albumin resulted in efficient albumin purification with reduced amount of contaminating proteins which lead to polymer formation during heat treatment (page 2, lines 27-32). The teaching of Matsuoka-1 et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

D) Neither Goodey et al. nor Matsuoka-1 et al. teach repeating AE chromoatography steps or affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

E) Regarding claims 83, 87, 138 and 140, Chang teaches repeating AE chromatography steps to remove contaminating proteins from albumin solution (Abstract; page 4, lines 17-39).

F) Regarding claims 83, 87, 138 and 140, Matsuoka-2 et al. teach albumin purification using ion exchange and affinity chromatography (Abstract). Matsuoka-2 et al. teach removal of α_1-acid glycoprotein from albumin preparation by affinity chromatography run in a negative mode with respect to albumin (col. 3, lines 38-68; col. 4, lines 1-24).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed α_1-acid glycoprotein by affinity chromatography of Matsuoka-2 et al. in the method of albumin purification by Goodey et al. and Matsuoka-1 et al. The motivation to do so, provided by Matsuoka-2 et al., would have been that α_1-acid glycoprotein was an impurity having immunosuppressive activity (col. 1, lines 44-46). Therefore, removing α_1-acid glycoprotein from albumin solution according to Matsuoka-2 et al. enhances the ability of Goodey et al. and Matsuoka-1 et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have repeated the AE steps in the albumin purification method of Goodey et al., Matsuoka-1 et al. and Matsuoka-2 et al. according to Chang. The motivation to do so, provided by Chang, would have been that repeating AE steps resulted in albumin purity of greater than 99% (page 4, lines 44-46).

16. Claims 122, 123, 126 and 127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946)) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action)) and Matsuoka-2 et al. (U.S. Patent No. 5,277, 818), as applied to claims 82 and 86 above.

A) Teachings of Goodey et al., Matsuoka-1 et al., Cohn et al., Shaklai et al. and Matsuoka-2 et al. are presented above. Matsuoka-1 et al. teach the concentration of albumin subjected to cation exchange chromatography being about 80 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 122 and 126) or albumin concentration of 50 $\pm$ 10 g/L (claims 123 and 127). However, the upper values of these ranges are very close to the 80 g/L value of Matsuoka-1 et al.

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference

process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 80 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka-1 et al.

17. Claims 124, 125, 128 and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Matsuoka-1 et al. (EP 0 428 758; cited in the IDS) (as evidenced by Cohn et al. (J. Am. Chem. Soc., vol. 68, pp. 459-475, 1946) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited

in the previous office action)), Matsuoka-2 et al. (U.S. Patent No. 5,277, 818) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Teachings of Goodey et al., Matsuoka-1 et al., Cohn et al., Shaklai et al., Matsuoka-2 et al. and Chang are presented above. Matsuoka-1 et al. teach the concentration of albumin subjected to cation exchange chromatography being about 80 g/L, but do not specifically teach albumin concentrations of 20-70 g/L (claims 124 and 128) or albumin concentration of 50 $\pm$ 10 g/L (claims 125 and 129). However, the upper values of these ranges are very close to the 80 g/L value of Matsuoka-1 et al.

B) Optimization of conditions for performing a process is considered to be a routine experimentation and differences in conditions as compared to prior art do not support patentability of the process (see MPEP 2144. 05 IIA):

MPEP 2144.05

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum

> combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, an ordinary practitioner would have recognized that the results optimizable variable of albumin concentration subjected to cation exchange chromatography could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific albumin concentration around 80 g/L was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the results of Matsuoka-1 et al.

18. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 8, 2005

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PATENT EXAMINER
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